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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SWITZER, JULIET CAROLINE	
ART UNIT	**PAPER NUMBER**
1634	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/19/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/617,453	CASPI ET AL.	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *1/22/07*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *14-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/22/07*.,
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This office action is written in response to applicant's papers received 1/22/07. The amendments and arguments presented in the papers have been carefully considered but are not persuasive to place the application in condition for allowance for the reasons set forth in this office action. **This action is FINAL.**

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A method of assessing a human subject for a predisposition to conduct disorder, committing a violent offense, a disposition towards violence or symptoms antisocial behavior, the method comprising the steps of

determining whether the subject carries a two or three repeat allele of a variable number tandem repeat polymorphism within the gene encoding human monoamine oxidase A enzyme, wherein the locus of said promoter is amplified using instant SEQ ID NO: 1 and SEQ ID NO: 2,

determining whether the subject has experienced childhood maltreatment, and

concluding that the subject is predisposed to conduct disorder, committing a violent offense, a disposition towards violence or symptoms antisocial behavior, if the subject carries the a two or three repeat allele and if the subject has experienced the environmental risk factor, does

not reasonably provide enablement for methods for predicting predisposition in non-humans, methods which consider associations between other polymorphisms within MAOA or polymorphisms in other genes that may be linked to expression of MAOA and these or other phenotypes, methods which predict predisposition to additional phenotypes, or methods which relate other environmental risk factors to these or additional phenotypes. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The instant claims are further broadly drawn to assessing a predisposition to any "mental disorder phenotype having an association with an at risk allele of a gene that encodes monoamine oxidase A enzyme, the association being conditioned by a pathogenic environmental risk factor status condition" a group of possible disorders which the specification teaches includes juvenile conduct disorder, antisocial personality disorder, psychosis, depression, anxiety, dementia, reading disability (¶ 0015 and ¶0016), but is also sufficiently broad to include any other possible disorder phenotype that is a behavorial, emotional or cognitive disorder, including learning delays, alcoholism, bipolar disorder, and a variety of additional phenotyes that are not joined by any particular cause, symptom or eteiology, but are all "mental disorder phenotypes" of one type or another. The specification provides no guidance as to which of these particular phenotypes, other than conduct disorder, committing a violent offense, a disposition towards violence or symptoms antisocial behavior, might have an association with an "at risk" allele of the MAOA gene where that association is conditioned by a pathogenic environmental risk.

Further, the scope of the "pathogenic environmental risk" set forth in the claims is extremely broad, including any possible pathogenic environmental risk, including, for example, childhood maltreatment, psychological trauma, psychosocial stress, unhealthy diet, infectious agents, toxic agents pharmacological agents, medical trauma and injury, as set forth in claims 6 and 7. Even these particularly listed risks are themselves broad, for example, medical trauma could include heart attacks, stab wounds, burst appendix, and a wide variety of other possible traumas.

The claims are broad with regard to the nature and identity of the "as-risk allele" of a gene that encodes MAOA enzyme, providing only the functional requirement that it is characterized by a low activity level of the enzyme. Such an allele could include truncations, deletions, substitutions, repeats, and any other possible genetic alterations.

Thus, the scope of the claims is quite broad. The nature of the invention requires the knowledge of an association between an allele of the MAOA enzyme gene an a particular phenotype, wherein that association is conditioned by a risk factor, in order to predict a predisposition to that phenotype. The claims specifically require that the mental disorder phenotype whose predisposition is assessed has an association with an at risk allele such that the association is "conditioned" by a pathogenic environmental risk factor status condition.

The specification does not provide any working examples where the method of the claimed invention is actually practiced, that is, where the method is used to assess the predisposition of an individual. The specification, however, exemplifies a relationship between one possible environmental risk factor, namely childhood maltreatment in males, and the mental disorder phenotypes conduct disorder, committing a violent offense, a disposition towards

violence or symptoms antisocial behavior (see pages 11-16 of the specification). These pages of the specification focus exclusively on a relationship that involves the examination of a single polymorphic location, that is a polymorphism variable number tandem repeat polymorphism that is known to effect expression. The specification does not provide the identity of any additional polymorphisms that are known to effect expression of this gene or that are associated with the studied mental disorder phenotypes, in humans or in other animals. The specification does not provide any data or guidance as to the relationship between the polymorphism studied and additional mental disorder phenotypes or risk factors.

There is a high degree of unpredictibilty regarding the association of polymorphisms within the MAOA enzyme encoding gene and mental disorder phenotypes. The state of the prior art does not provide any data or evidence regarding another association that is "conditioned" by a particular risk factor. The prior art does however demonstrate many instances where practitioners attempted to establish relationships between polymorphisms within MAOA and mental disorder phenotypes and failed. For example, Wei et al. teach that they observed no significant differences in frequency of alleles a microsatellite repeat in MAOA between controls and subjects with schizophrenia (Wei et al. Eur Psychiatry 1998, Vol. 13, pages 407-410). Hamilton et al. (Molecular Psychiatry, 2000, Vol. 5, pages 465-466) teach that they found no genetic linkage or association between a polymorphism in the MAOA promoter and panic disorder. Norton et al. studied a single nucleotide polymorphism and a VNTR polymorphism in the MAOA gene and found no evidence for association with schizophrenia (Norton et al. American Journal of Medical Genetics (Neuropsychiatric Genetics) 2002,114:491-496). Additional attempts were made to associate genotypes of the MAOA gene with completed

suicides, manic-depressive illness, bipolar disorder, and unipolar disorder, but these were unsuccessful (Ono et al. American Journal of Medical Genetics (Neuropsychiatric Genetics) 2002, 114:340-342; Parsian et al. American Journal of Medical Genetics (Neuropsychiatric Genetics) 1997, 74:475-479; and Kungi et al. Molecular Psychiatry, 1999, Vol. 4, 393-395). These studies together exemplify the high degree of unpredictability in this subject area. The lack of guidance in the specification regarding the application of the claimed methods using additional genotypes with MAOA to different phenotypes with different risk factors is particularly difficult to overcome in view of such a high degree of unpredictability in the prior art.

Thus, having carefully considered all of these factors, it is concluded that the specification is not sufficient to enable one to make and use the invention commensurate in scope with the instant claims.

Response to Remarks

The rejection under 102(a) was overcome by the filing of a 1.132 declaration.

Applicant traverses the 112 1st rejection for scope of enablement. Applicant's amended the claims to recite that the subject is human. This aspect of the rejection is overcome. Applicant traverses the remainder of the rejection.

Applicant points to the discussion of unpredictability at the end of the rejection and points out that those references are discussing direct gene to disorder effects while the instant claims recite determining whether the subject has experienced a risk factor as part of the method. Nonetheless, the cited references are germane to the discussion of the level of unpredictability in this technology area. The claims are extremely broad in scope with regard to

potential associations between MAOA alleles and any possible mental disorder phenotypes and environmental risks, and so, the related cited references are relevant to the high degree of unpredictability in this technology area.

Applicant state that they demonstrated that low activity level conditioned by experience (or risk of experience) permits assessment of a predisposition to a mental disorder phenotype. On the contrary, applicant showed that a single polymorphism permits such assessment. Applicant did not do a direct measure of the subjects MAOA activity levels. The relationship between the polymorphism and MAOA is predictive but not clearly delineating. Further, it was not established that the mental disorder phenotype is caused by low MAOA activity. This is possible, but it is also possible that the examined polymorphism is linked to some other gene which is causative of the association. There is no written description of other polymorphisms within MAOA that are related to the disclosed mental disorder phenotype. Each of these aspects of determination are highly unpredictable. The scope of the claim regarding the polymorphism used in the assay would require the discovery of additional polymorphisms within MAOA, the analysis of these polymorphisms to establish their relationship to MAOA activity, and then their analysis to establish if they are related to the human mental disorder phenotypes and conditioning experiences in the same fashion as those factors set forth in the examples. As discussed in the rejection, each of these is a highly unpredictable area with little or no specific guidance given in the specification.

Applicant points out that the claims embrace mental disorder phenotypes having an association with an at-risk allele of a gene that encodes MAOA (p. 9), and that the specification teaches that DSM-IV can be used to determine mental disorder phenotypes. However, it remains

that there is no specific guidance given in the specification as to what further combinations of mental disorder phenotypes and pathogenic risk factors are related and mediated by MAOA alleles. Given the breadth of the claims and the unpredictability of this technology area, significant guidance would be needed to practice the claimed invention commensurate in scope with the claims.

Applicant states that because psychology and psychiatry are such "fluid" fields of study that the artisan therefore accepts some uncertainty as to the precise impact of environmental factors and is therefore accustomed to spending time and effort discovering environmental risk factors associated with particular mental diseases. This is an attorney arguments which is not supported by evidence on the record. Even if it were, however, the idea that practitioners in this field are accustomed to spending time discovering environmental risk factor/disease associations does not remove the unpredictability of this endeavor from the issues at hand. In addition, the practice of the claims commensurate in scope require a number of layers of unpredictable discovery, not only the relationship between diseases and environmental risk factors, but further that the association of a gene and the phenotype is "conditioned" by the risk factor. Each step requires extensive screening, research and experimentation, and each step is a priori unpredictable.

Applicant notes the study the current application was based upon was replicated by other groups. The examiner did not question the study in the specification, but the scope of the claims that is not commensurate with the study.

Applicant points to additional post-filing references which look at other disease phenotypes conditioned upon pathogenic risks and related to polymorphic genotypes. The

studies in these references are not within the scope of the claims. Also, these references are not prior art relative to the instant application. Therefore these references do not support applicant's arguments that the specification was sufficient to enable the claimed invention at the time of filing since MPEP 2124 states,

> "...it is impermissible to use a later factual reference to determine whether the application is enabled or described as required under 35 U.S.C. 112, first paragraph. In re Koller, 613 F.2d 819, 823 n. 5, 204 USPQ 702, 706 n.5 (CCPA 1980). References which do not qualify as prior art because they postdate the claimed invention may be relied upon to show the level of ordinary skill in the art at or around the time the invention was made. Ex parte Erlich, 22 USPQ 1463 (Bd. Pat. App. & Inter. 1992)."

The rejection is **MAINTAINED**.

Conclusion

4. No claim is allowed.

5. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Monday, Tuesday, or Thursday, from 9:00 AM until 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached by calling (571) 272-0735.

The fax phone numbers for the organization where this application or proceeding is assigned are (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-0507.

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general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Juliet C. Switzer
Primary Examiner
Art Unit 1634

April 16, 2007